PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C07K 16/00, 16/42, A61K 39/00, 39/385, 39/395, G01N 33/577, 33/68, A61P 37/08

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9910537.1	7 May 1999 (07.05.99)	GB
9910538.9	7 May 1999 (07.05.99)	GB
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9927698.2	23 November 1999 (23.11.99)	GB

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DYSON, Michael [GB/GB]; Peptide Therapeutics Limited, Peterhouse Technology Park, 100 Fulbourn Road, Cambridge CB1 9PT (GB). FRIEDE, Martin [GB/GB]; Corporate Intellectual Property, SmithKline Beecham, 2 New Horizons Court, Brentford, Middlesex TW8 9EP (GB). GREENWOOD, Judith [GB/GB]; Peptide Therapeutics Limited, Peterhouse Technology Park, 100 Fulbourn Road, Cambridge CB1 9PT (GB). HEWITT, Ellen [GB/GB]; Peptide Therapeutics Limited, Peterhouse Technology Park, 100 Fulbourn Road, Cambridge CB1 9PT (GB). LAMONT, Alan [GB/GB]; Peptide Therapeutics Limited, Peterhouse Technology Park, 100 Fulbourn Road, Cambridge CB1 9PT (GB). MASON, Sean [GB/GB]; Peptide Therapeutics Limited, Peterhouse Technology Park, 100 Fulbourn Road, Cambridge CB1 9PT (GB). RANDALL, Roger [GB/GB]; Peptide Therapeutics Limited, Peterhouse Technology Park, 100 Fulbourn Road, Cambridge CB1 9PT (GB). TURNELL, William, Gordon [GB/GB]; Peptide Therapeutics Limited, Peterhouse Technology Park, 100 Fulbourn Road, Cambridge CB1 9PT (GB). VAN MECHELEN, Marcelle, Paulette [BE/BE]; SmithKline Beecham Biologicals s.a., rue de l'Institut 89, B–1330 Rixensart (BE). VINALS Y DE BASSOLS, Carlota [BE/BE]; SmithKline Beecham Biologicals s.a., Rue de l'Institut 89, B–1330 Rixensart (BE).

(74) Agent: DALTON, Marcus, Jonathan, William; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: EPITOPES OR MIMOTOPES DERIVED FROM THE C-EPSILON-2 DOMAIN OF IGE, ANTAGONISTS THEREOF, AND THEIR THERAPEUTIC USES

(57) Abstract

The present invention relates to the provision of novel medicaments for the treatment, prevention or amelioration of allergic disease. In particular, the novel medicaments are isolated peptides incorporating epitopes or mimotopes of surface exposed regions of the Cε2 domain of IgE. The inventors have found that these novel regions may be the target for both passive and active immunoprophylaxis or immunotherapy. The invention further relates to methods for production of the medicaments, pharmaceutical compositions containing them and their use in medicine. Also forming an aspect of the present invention are ligands, especially monoclonal antibodies, which are capable of binding the surface exposed IgE regions of the present invention, and their use in medicine as passive immunotherapy or in immunoprophylaxis.

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 October 2000 (04.10.00)	
International application No. PCT/EP00/01455	**Applicant's or agent's file reference** RE/B45172
International filing date (day/month/year) 22 February 2000 (22.02.00)	**Priority date** (day/month/year) 25 February 1999 (25.02.99)
Applicant DYSON, Michael et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   01 August 2000 (01.08.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
SMITHKLINE BEECHAM
Attn. Dalton, Marcus Jonathan
Two New Horizons Court
Brentford
Middlesex TW8 9EP
UNITED KINGDOM

Applicant's or agent's file reference RE/B45172	Date of mailing *(day/month/year)* 04/08/2000 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 00/ 01455	International filing date *(day/month/year)* 22/02/2000
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41–22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Catherine Humbert

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
RE/B45172		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 01455	22/02/2000	25/02/1999
Applicant		
SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

EPITOPES OR MIMOTOPES DERIVED FORM THE C-EPSILON-2 DOMAIN OF IGE, ANTAGONISTS THEREOF, AND THEIR THERAPEUTIC USES

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01455

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/00 C07K16/42 A61K39/00 A61K39/385 A61K39/395
G01N33/577 G01N33/68 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
STRAND, CHEM ABS Data, MEDLINE, LIFESCIENCES, CANCERLIT, AIDSLINE, EMBASE, SCISEARCH, EPO-Internal, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAKIB F ET AL: "Elucidation of the epitope locations of human autoanti-IgE: recognition of two epitopes located within the C epsilon 2 and the C epsilon 4 domains." INTERNATIONAL ARCHIVES OF ALLERGY AND APPLIED IMMUNOLOGY, (1991) 95 (2-3) 102-8. , 1991, XP000929202 page 102, right-hand column, line 9 page 103, left-hand column, line 1-5 page 105, right-hand column, line 3 -page 107, left-hand column, line 5,28-44 figures 1,5 --- -/--	1-11,22, 27, 30-32,36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2000	04/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Covone, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 171 299 A (HAMBURGER ROBERT N) 16 October 1979 (1979-10-16) column 2, line 64 -column 3, line 3 column 3, line 14-23 column 5, line 49-55	1,2,4,5, 9-12,27, 30,39
X	WO 99 04265 A (SAHIN UGUR ;TURECI OZLEM (DE); PFREUNDSCHUH MICHAEL (DE); GOUT IVA) 28 January 1999 (1999-01-28) page 85, line 43	2,12
A	WO 98 24808 A (UNITED STATES DEPT. OF HEALTH AND HUMAN SERVICES, USA;PADLAN, EDUARDO) 11 June 1998 (1998-06-11) page 3, line 10-24 page 4, line 21-23 page 11, line 16-29	1-41
A	HEUSSER C ET AL: "Therapeutic potential of anti-IgE antibodies." CURRENT OPINION IN IMMUNOLOGY, (1997 DEC) 9 (6) 805-13. REF: 76 , 1997, XP002125679 page 805, right-hand column, paragraph 2 page 807, left-hand column, paragraphs 3,4 page 811, right-hand column, paragraph 3	1-41

Continuation of Box I.1

Although claims 34 (partially) 37 (completely) are directed to a diagnostic method practised on the human/animal body, and claims 39-41 (completely) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Present claims 1-9 encompass mimotopes which compounds have only been defined by reference to a desirable characteristic or property, namely any entity which when formulated into an immunogen, is capable of inducing an immune response, which response is capable of recognising the peptides disclosed (see page 6 of the application). The claims cover all products and compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products and compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define a compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products and compounds disclosed in claims 13, 14, 15 and 16.
Further the initial phase of the search for the subject-matter of claim 12 revealed more then 100 sequences corresponding to more then 50 documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim 12 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim is impossible. Consequently, the search has been restricted to those parts of the claim 12 which appear to be supported and disclosed, namely those parts relating to the products having the properties disclosed in claim 13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

X

see FURTHER INFORMATION sheet PCT/ISA/210

X -

see FURTHER INFORMATION sheet PCT/ISA/210

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/01455

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4171299 A	16-10-1979	AU 514308 B	05-02-1981
		AU 1230376 A	29-09-1977
		BE 840193 A	30-09-1976
		CA 1087171 A	07-10-1980
		CA 1079721 A	17-06-1980
		CH 624093 A	15-07-1981
		DE 2602443 A	21-10-1976
		FR 2305989 A	29-10-1976
		GB 1539102 A	24-01-1979
		JP 1278969 C	29-08-1985
		JP 51118702 A	18-10-1976
		JP 60002318 B	21-01-1985
		MX 3790 E	20-07-1981
		NL 7603384 A	06-10-1976
		SE 430058 B	17-10-1983
		SE 7603897 A	05-10-1976
		US 4161522 A	17-07-1979
WO 9904265 A	28-01-1999	US 6043084 A	28-03-2000
		AU 8571598 A	10-02-1999
		EP 0996857 A	03-05-2000
WO 9824808 A	11-06-1998	AU 6532498 A	29-06-1998

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
RE/B45172		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/01455	22/02/2000	25/02/1999
International Patent Classification (IPC) or national classification and IPC C07K16/00		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/08/2000	20.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hoesel, H Telephone No. +49 89 2399 8693

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/01455

I. Basis f the rep rt

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-57 as originally filed

Claims, No.:

1-41 as originally filed

Drawings, sheets:

1/37-37/37 as originally filed

Sequence listing part of the description, pages:

1 - 31, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application; the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1 - 9, 12, 39 - 41.

because:

   ☒ the said international application, or the said claims Nos. 39 - 41 for IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1 - 9, 12 (all partially) are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1 - 9, 12 (all partially).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12 - 16, 18, 23, 32 - 34, 37, 41
	No:	Claims	1 - 11, 17, 19 - 22, 24 - 31, 35, 36, 38 - 40
Inventive step (IS)	Yes:	Claims	12 - 14, 41
	No:	Claims	1 - 11, 15 - 40 (no)
Industrial applicability (IA)	Yes:	Claims	1 - 38
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain obs rvations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: US-A-4,171,299
D2: WO-A-93/05810
D3: WO-98/24808
D4: Helm et al, PNAS vol. 86, 1989, p. 9465- 9469
D5: Wang et al, Eur. J. Immunol. vol. 26, 1996, p. 1043 - 1049
D6: Shakib & Powell-Richards, Int Arch Allergy Appl Immunol vol. 95, 1991, p. 102 - 108

SECTION I:

1. The sequence listing comprising pages 1 - 31 as originally filed has been taken into account as a basis of this opinion.

SECTION III:

2. The wording "mimotope" redundantly used in the claims leaves the reader in doubt as to relevant structural characteristics of the said compound, such as size of the fragment, which and how many amino acid residues are to be substituted and which are the respective substituents. Taking account of the tantamount of possibilities to modify a single peptide, the vast majority of which will significantly impair or destroy its original binding characteristics, the wording "mimotope" does not allow a skilled person to identify suitable derivatives without extensive burden and application of inventive skill.

   Claims 1 - 9 are thus considered not to be enabled in the sense that they cannot be carried out over the whole field claimed, contrary to Art. 5 PCT, with respect to the obscure concept of "mimotopes".

   The examination of the said claims has therefore been limited to those peptides /mimotopes that have been described by way of a defined sequence, i.e. insofar as their scope has been searched by the international searching authority.

3. Having regard to the indicated structural concept, claim 12 encompasses about 2

x 10^9 potential peptide sequences. Only a few of them will act in respect of their binding capability to the selected antibodies and in their capability to exert antiallergic activity as "P1 mimotope".

Assessment of claim 12 with respect to novelty and inventive step is therefore limited to those sequences which are supported by the description.

4. Claims 39 - 41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION IV:

5. The common concept linking together the various independent claims may be formulated to provide IgE peptides comprising at least parts of the cε2 domain and antibodies specific thereto.

Peptides that contain parts of cε2 domain including surface exposed epitopes, as demonstrated by the capability to be recognized by domain specific antibodies, alone or in conjunction with parts of or the entire the Cε3 have been described and additionally suggested for use in the treatment allergies (see Section V, items 6 and 7).

Also cε2 domain specific antibodies that necessarily react with surface exposed structures/epitopes have been described (Section V, item 9).

Thus the common concept, is neither novel nor inventive.

Hence, the international examining authority considers that the following separate inventions or groups of inventions are not so linked as to form a single general inventive concept (Rule 13bis PCT).

1: Oligopeptides that express the isolated P1 epitope, ligands thereto and their uses,

2. - 7: Oligopeptides that express exclusively the cε2 domain epitopes identified as P2 - P7

SECTION V:

6. D1 discloses peptides derived from the IgE cε2 domain which correspond to aa276 - 298, aa299 - 322 and aa323 - 346 (col. 3, lines 9 - 22). Furthermore, oligopeptides corresponding to aa276 - 280, aa266 - 285, aa281 - 285 and aa209 - 304 have been synthesized and tested for antiallergic activity.

   Thus, D1 anticipates the subject-matter of claims 1 - 4, especially insofar as fragments of the given sequences that still act as a mimotope are concerned. D1 is furthermore detrimental to the products as broadly covered by present claims 9 - 11, 27 as well as the uses and methods according to claims 30 and 39, contrary to Art. 33(2) PCT.

7. Having regard to the non-limiting wording "comprising", claim 1 extends to human IgE heavy chain fragments that contain parts of or the entire cε2 domain alone or in conjunction with neighbouring domains. Such peptides have been described in various instances in the prior art as is discussed in the description.

7.1. The peptides as disclosed in D2 (see the abstract and claim 1), for instance, fall within the scope of claims 1 to 11, contrary to Art. 33(2) PCT. D2 furthermore discloses coupling of the peptides to carrier proteins, expression as fusion protein, vaccines comprising such immunogens and the use of the products for the treatment of allergies (D2, claims 2 - 10).

   In the absence of a clear limitation of claims 1 - 9, D2 therefore also anticipates the subject-matter of claims 17, 19 - 21, 27 - 30, 35, 36, 38 - 40.

7.2. At present also the fusion products investigated in D3 (cf. Fig 1 A) or D4 which describe fragments comprising the entire cε2 domain or C-terminal parts thereof (particularly the fragments aa218 - 362 and aa301 - 376, see p. 9465, col. 2, lines 13 - 16 and lines 26 - 31) are detrimental to the novelty of claims 1 - 9, 17, 19 and 20.

7.3. D5 describes tolerogenic fragments of murine IgE that contain the N-terminal half or the major parts of the cε2 domain (abstract, p. 1046, fig 3, fragments F and I)

These fragments are considered to fall within the scope of present claims 1 - 11, in view of the vague and obscure concept of "mimotope" which can be interpreted to encompass murine analogues of human cε2 domain derived epitopes.

8. If claims 1 - 9 are limited so as to be novel, the following has to be noted:

Methods of identifying and mapping epitopes within a given protein by way of monoclonal antibodies or by analysis of the primary sequence for stretches of increased hydrophilicity is commonly known. In view of the length of the cε2 domain, the identification of discrete epitopes can be expected. In D6 it is explicitly, suggested to produce such "short synthetic peptides representative of solvent-accessible" (i.e. epitopic) "parts" of the cε2 and 4 domains in order to map the epitope specificity of human anti-IgE antibodies (see D6, the sentence extending between p. 107 and 108). The identification and preparation of corresponding peptides are therefore not considered to be inventive unless a particular regulatory and exploitable activity can be contributed with such epitopes.

Having regard to the experimental part, such an activity (lack of anaphylactogenicity and capability of inhibiting allergen-induced responses) has been found only for the P1 epitope and some particular structures related therewith.

For these particular peptides (the P1 peptide and functional equivalents thereof) inventive step could be acknowledged. In the absence of evidence for an antiallergic activity, the peptides according to claims 2 - 7 are considered to lack an inventive step, contrary to Art. 33(3) PCT.

9. Antibodies that bind in a domain specific manner to native IgE, including those binding to the cε2 domain have been disclosed in the prior art (see D3, p. 31, lines 24/25) and are commercially available (sold by Sigma). Necessarily such antibodies react with surface-exposed epitopes of the said domain.

Thus, the subject-matter of claim 22 lacks novelty in view of D3 (Art. 33(2) PCT)

The objection analogously applies to claims 24 - 26, as the compositions of these claims are defined as having the (known) antibody as the single constituent and thus cannot be distinguished from commercially available pure preparations of PTmab0005.

10. It is demonstrated that the monoclonal antibody of claim 23 is an equivalent to one which has been commercially available for years as regards the epitope specificity.

    Consequently the said antibody is not considered as inventive in the sense of Art.33(3) PCT.

11. Claims 16, 34 and 37 concern conventional design options in the field of vaccine preparation or conventional uses of monoclonal antibodies. The claims are therefore considered to lack an inventive step, contrary to Art. 33(3) PCT.

12. The prior art is silent as to a regulatory function of the P1 epitope in mediating allergic responses. Thus, claims directed to a medical use of the said peptide or immunogens derived therefrom - if they were satisfactorily limited (see item 7) - or specific antibody ligands could be considered as novel and inventive.

13. For the assessment of medical use claims, i.e. present claims 27 - 33 and 39 - 41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VII:

14. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art

disclosed in the documents D1, D2 and D6 is not commented on in the description, nor are these documents identified therein.

15. The international examining authority is aware of two co-pending applications claiming the same priority date (pct/ep00/01456 and pct/ep00/01457). It appears that these applications claim at least parts of the subject-matter covered by the present claims. In view of the widely accepted principle that two patents shall not be granted to the same applicant for the same invention, the applicant might be required in the national phase to limit the claims in the different applications or to choose which one of these applications should be pursued for a grant (cf. PCT-Guidelines C-IV-6.2).

SECTION VIII:

16. According to D6, anti-IgE antibodies binding to the cε2 domain have been identified in sera of patients suffering from allergic diseases. It is emphasized that antibodies binding to the C-terminal parts of cε2 domain might exert a pro-allergic effect by crosslinking receptor bound IgE. Such an activity would contraindicate a therapeutic use.

The present application provides evidence for a lack of anaphylactogenicity and a desired anti-allergic activity for P1 peptides and antibodies specific thereto only. In view of the disclosure of D6, an analogous use of the other isolated P2 to P7 oligopeptides must be drawn in question.

Thus, the claims directed to a medical use are considered not to be sufficiently supported, contrary to Art. 6 PCT, insofar as these compounds (P2 - P7 oligopeptides and antibodies specifically binding therewith) are concerned.

17. Although claims 2/35 and 17/36 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent

claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, the said claims do not meet the requirements of Article 6 PCT.